AUSTRALIA

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OVERVIEW AND USE

Australia is a vast island continent with a unique flora and fauna. The economy is dependent on bulk commodity exports, and agricultural exports accounted for approximately A$29 billion in 2009, or 4.6% of total exports (Australian Bureau of Agricultural and Resource Economics 2010). However, the Australian pesticide market is small, estimated to be about 2-3% of the total global market for pesticides.

Early experiments with microbial control included field trials in the late 1960s with the granulosis virus of codling moth in apple orchards, and in the 1970s with Elcar, the nucleopolyhedrosis virus (NPV) of *Helicoverpa zea*. Initial success was limited, with poor field efficacy and direct competition with new chemical insecticides. Early large scale field trials with the granulosis virus of potato tuber moth, *Phthorimaea operculella*, gave promising results (Reeda and Springetta 1971), but a commercial product was not registered.

The number of microbial pesticides registered in Australia has increased in the last decade (Table 18), with the widescale use of *Bacillus thuringiensis* subsp. *kurstaki* (Btk). A crisis in insecticide resistance in *Helicoverpa* species in the late 1990s led to adoption of area-wide integrated pest management in the commercial cotton and sorghum industries, where biopesticides are used to manage resistance to chemical insecticides and to reduce secondary pest outbreaks (such as silver leaf white fly) by maintaining beneficial insect populations. Biopesticides are also used in areas of special concern such as national parks, in the expanding ‘organic’ market, and for export markets such as wine, where the industry restricts the use of synthetic insecticides (Hunter 2010).

The biopesticides market is dominated by Btk products for control of a range of lepidopteran pests, and Bt genes have been incorporated into cotton crops to manage *Helicoverpa* spp. Btk was adopted by the grape and wine industry to control light brown apple moth (*Epiphyas postvittana*), a native tortricid moth. The introduction of Btk in place of broad-spectrum insecticides resulted in a significant reduction in frequency of outbreaks of light brown apple moth in grape vines, presumably as a result of maintenance of natural enemies. *B. thuringiensis* subsp. *israelensis* (Bti) is also used for control of nuisance biting insects and disease vectors in coastal mangroves and housing areas, where application of chemical insecticides is unacceptable.

The success of Bt also demonstrated the importance of good product supply and quality, and established supply chains on which growers could depend. This was also a key factor in success of biopesticides based on NPVs. The brief success with Elcar in the 1970s supported continued research in baculoviruses by the Queensland Department of Primary Industries. Interest was renewed in the late 1990s in the face of a crisis in management of insecticide resistance in *Helicoverpa armigera* and escalating costs of insecticides. The biopesticide 'Gemstar' based on *H. zea* NPV was imported from the USA, and initial trials were conducted under a special permit. The product was registered for use in cotton and sorghum in 1999.

Table 18. Microbial pesticides registered in Australia.

	Taxus	Products	Targets
Bactericides			
Agrobacterium radiobacter	Bacterium	NoGall	Crown gall disease
Fungicides			
Trichoderma harzianum	Fungus	Trichodex Vinevax	*Botrytis* spp. *Eutypa* dieback
Insecticides			
Bacillus sphaericus	Bacterium	VectoLex	Mosquito larvae
Bacillus thuringiensis subsp. a*izawai*	Bacterium	Agree Bacchus XenTari	Lepidoptera larvae
Bacillus thuringiensis subsp. *israelensis*	Bacterium	Aquabac BTI Teknar Vectobac	Mosquito larvae
Bacillus thuringiensis subsp. *kurstaki*	Bacterium	Biocrystal Caterpillar Killer DiPel Costar Delfin Full-Bac WDG	Lepidoptera larvae
Metarhizium anisopliae	Fungus	BioCane Granules	Grey-backed cane grub (scarabs)
Metarhizium anisopliae subsp. *acridum*	Fungus	Green Guard	Locusts and grasshoppers
Metarhizium flavoviride	Fungus	Chafer Guard	Redheaded pasture cockchafer
Helicovera armigera nucleopolyhedrosis virus	Virus	Heliocide Vivus Gold Vivus Max	*Helicoverpa* spp.
Helicovera zea nucleopolyhedrosis virus	Virus	Gemstar Vivus	*Helicoverpa* spp.

Demand for NPV was such that in 2000, Ag Biotech Australia established a pilot plant to produce *Helicoverpa* NPV in Australia. The initial product was produced in *H. armigera* using the American isolate from *H. zea* and was branded Vivus. The first commercial sales of Vivus were made in 2003. The American virus strain was then replaced with a native *H. armigera* strain, isolated many years previously by the Queensland Department of Primary Industries and Fisheries, and Vivus Gold was registered in 2004.

Helicoverpa spp. are a major pest of many crops, and the NPV products are now have registered on a broad range of crops including sorghum, cotton and horticultural crops. Around 500,000 hectares of crops were treated in 2008. Vivus Gold is now also registered for application through 'centre pivot' irrigation, a method that has proven to be very successful by a number of innovative sweet corn producers. A concentrate product, Vivus MAX is now registered, containing over twice the number of virus occlusion bodies as previously, thus reducing packaging and improving storage and distribution.

The first fungal insecticide was manufactured and registered in Australia by BioCare Ltd. in 2000. 'BioGreen' (now 'Chafer Guard'), based on *Metarhizium flavoviride*, is a granular product consisting of broken rice on which the fungus is grown and sporulates. It is used to control redheaded pasture cockchafer, *Adoryphorus couloni*, in turf and pasture (Milner 2000). The second product, also registered by BioCare, was 'BioCane' containing *M. anisopliae* for control of greyback canegrub (*Dermolepida albohirtum*). Becker Underwood Pty Ltd. now manufactures both products in Australia.

Metarhizium anisopliae subsp. *acridum* was first evaluated for plague locust control under a collaboration between CSIRO and the UK Commonwealth Agriculture Bureau (CABI) in 1998. An Australian isolate with good production and control characteristics was identified and used initially under a special permit in national parks and 'organic' beef rangeland by the Plague Locust Commission (Milner 2000). The product was registered in 2005 as Green Guard, also manufactured by Becker Underwood, and has been applied to over 100,000 ha between 2000 and 2009 (Hunter 2010).

The success of biopesticides in crops and in locust control has led to significant research in potential controls for emerging pests such as mirids and aphids, particularly in genetically modified Bt cotton, which is susceptible to sucking pests. Trial results have shown good control of aphids and mirids in cotton and pulse crops with native isolates of *M. anisopliae* (Hauxwell, *unpublished*). *M. anisopliae*, *Beauveria bassiana* and *Verticillium lecanii* have also been tested in glasshouse trials (Goodwin and Steiner 2002), though are not currently registered. *M. anisopliae* has also been tested against cattle ticks and sheep lice by the Queensland Department of Primary Industries.

Considerable research has been conducted into use of nematodes against a wide range of pests (including snails, scarabs, weevils, gnats, sheep lice and wood wasps). However, nematodes are considered 'natural enemies' (along with, e.g., parasitoids and predators) if they are visible to the naked eye, and are thus exempt from registration and are not discussed in this review. Those species not visible to the naked eye are classed as microscopic and require registration, but none have been registered.

A small number of anti-microbial pesticides are registered, including *Trichoderma harzianum* against *Botrytis* and *Eutypa* dieback in vines. Becker Underwood has registered NoGall containing the bacterium *Agrobacterium radiobacter* for use against crown gall (caused by the soil bacterium *Agrobacterium tumefaciens*) in stonefruit and ornamental plants.

REGISTRATION AND THE REGULATORY SYSTEM

Registration of pesticides is governed by the Agricultural and Veterinary Chemicals Code Act 1994 and administered by the Australian Pesticides and Veterinary Medicines Authority (APVMA). The importation of a biological agent also requires authorisation from the Australian Quarantine Inspection Service (AQIS) prior to introduction into Australia. If the organism has been genetically altered, approval from the Office of the Gene Technology Regulator (OGTR) is required prior to importation or release.

Approval from APVMA must be obtained for any new active constituent (including an organism), and any new product and all proposed uses of the product must be registered by APVMA. The legislation requires, prior to registering any new product, APVMA to be satisfied that the product, if used in accordance with the instructions for its use:

- will not adversely affect human and animal health and safety,
- will be effective and of consistent quality,

- will not adversely affect the environment, and
- will not affect international trade in commodities.

The APVMA also has a Permit Scheme that allows for the use of pesticides in ways that are different to the uses set out on the product label or for limited 'emergency' use of an unregistered product. *M. anisopliae* var. *acridum* for locust control was initially used under permit, later going on to full registration. An application for a permit must satisfy the same criteria as for registration, though as the extent of use is intended to be small, the supporting data requirements and evaluation processes may be simpler. However, in practice, the stringent requirements can be as demanding as a full registration.

The APVMA's Manual of Requirements and Guidelines (MORAG) sets out the requirements for agricultural and veterinary chemicals to be manufactured or used in Australia (see references for links). The basic requirements for registration of microbial pesticides are the same as for chemical pesticides, including a comprehensive package of data on toxicology, efficacy, storage and (to some extent) field residues. Toxicology and residue analysis should be conducted in accordance with Good Laboratory Practice. Guidelines published in 2005 contain additional requirements for microbial pesticides to include evaluation of potential hazards such as toxin production, pathogenicity and infectivity, host range, and effects on native flora and fauna (APVMA 2005).

Active organisms must be fully characterised and their relationship to other organisms, particularly known pathogens, must be described. Any contaminating microorganisms or preparation by-products must also be identified, quantified and evaluated for pathogenicity, toxicity or persistence. Manufacturing methods and quality control procedures to limit contaminants must be described.

Toxicology testing is modelled on chemical pesticide testing, including requirements to evaluate lethal doses (LD50s) in mg per kg body weight. This may be practically impossible to determine for biological products that do not contain active chemical compounds. Long-term toxicological testing is not normally required unless, for example, the organism produces compounds of concern such as potentially carcinogenic metabolites.

Australian agriculture relies heavily on exports of agricultural commodities. Registration data must demonstrate that the product will not harm crops of importance or "prejudice trade or commerce between Australia and places outside Australia". This is rarely a concern for microbial pesticides, but the potential to affect trade through residues or viable organisms that remain in the commodity must be evaluated.

It is required to demonstrate that the formulated product of chemical pesticides will remain within specification for at least 2 years under typical storage conditions i.e. at around 30˚C in the product packaging. Where this cannot be achieved (as is the case with most microbial pesticides) they can be registered as 'date-controlled products' with an expiry date on the label. This may include a requirement for cool storage and transport. Vivus NPV products, for example, have an approved label with a shelf life of 2.5 years when stored at 4°C.

Residue data are normally not required for microbial agents unless the organism produces a metabolite of concern: if not supplied, an exemption must be requested with a sound scientific justification. Residue decline information is generally required when an application is expected to be made close to harvest (usually less than 14 days for most crops), or an application is made after harvest, or there are trade implications for the produce. However, the registration of Green

Guard followed the classic synthetic insecticide pathway, with stringent requirements for residue data.

Residue data may not be meaningful if, for example, there is a persistent, low-level occurrence of the organism in the environment from natural transmission. The short field persistence of some microbial pesticides can be an advantage in this regard. The Vivus range of NPV products, for example, have no withholding period.

APVMA normally requires efficacy data from trials conducted in Australia over at least two years and under a suitable range of pest pressures for each pest and crop combination specified on the label. This should include data from each of the major regions or environmental zones in Australia where the product will be used. Overseas data can be used to support an application if it is applicable to Australian uses and conditions, for example in controlled environments such as glasshouses where conditions are similar to those in Australia. Overseas data alone are rarely sufficient for registration, and thus approval for environmental release must be obtained in order to conduct tests in Australia.

Australia invests heavily in border protection to prevent the introduction of harmful or invasive species and protect its unique flora and fauna. Even endemic species may have adverse effects if introduced into other regions of Australia. Registration submissions for a microbial pesticide must include evaluation of persistence and replication of the organism, including its ability to induce epizootics, and its specificity or potential harmful effects on native flora and fauna prior to introduction into Australia.

The burden of determining effect on native non-target species can be significant, and it may be difficult to anticipate what testing may be requested following review. Non-target studies conducted overseas can be included, however, specific tests on Australian biota may be required where there are concerns about impact on wildlife, flora or ecosystems.

Addressing concerns on potential impact of a microbial pesticides on the Australian environment can be costly, time consuming and difficult. It may be possible to reduce the data required if it can be demonstrated that the agent/organism will not survive in the Australian environment, or if the organism will be effectively contained or is highly host specific. Even where the organism occurs in Australia, requirements for data on natural occurrence and distribution of the organism in Australia are stringent and can be difficult to meet.

The evaluation process

Following submission of an application, APVMA conduct an initial screen to ensure supporting data are complete, and conduct a preliminary evaluation. This may generate requests for further information on technical aspects of the application. After screening, a full evaluation is conducted and data are scrutinised by relevant experts, as outlined in Figure 4.

- Product characterisation, chemistry, production and quality control systems, and residues are assessed by experts within APVMA.
- Toxicology and occupational health and safety are evaluated by the Office of Chemical Safety and Environmental Health (within the Department of Health and Aging).
- Environmental fate and effects are evaluated by the Environment Protection Branch of the Department of Environment, Water, Heritage and Arts.
- Efficacy and stability are evaluated by external experts (usually research scientists) selected by APVMA.

A public consultation process is conducted. Comments are sought from other departments and authorities (such as The Office of the Gene Technology Regulator or the National Health and the Medical Research Council and state departments of agriculture) and public comment is invited through a notice in the Agricultural and Veterinary Chemicals Gazette (available from the APVMA website). A summary of planned approvals is sent to interested members of the public and relevant industry bodies for comment. All comments are considered before the final decision on whether to register the product is made.

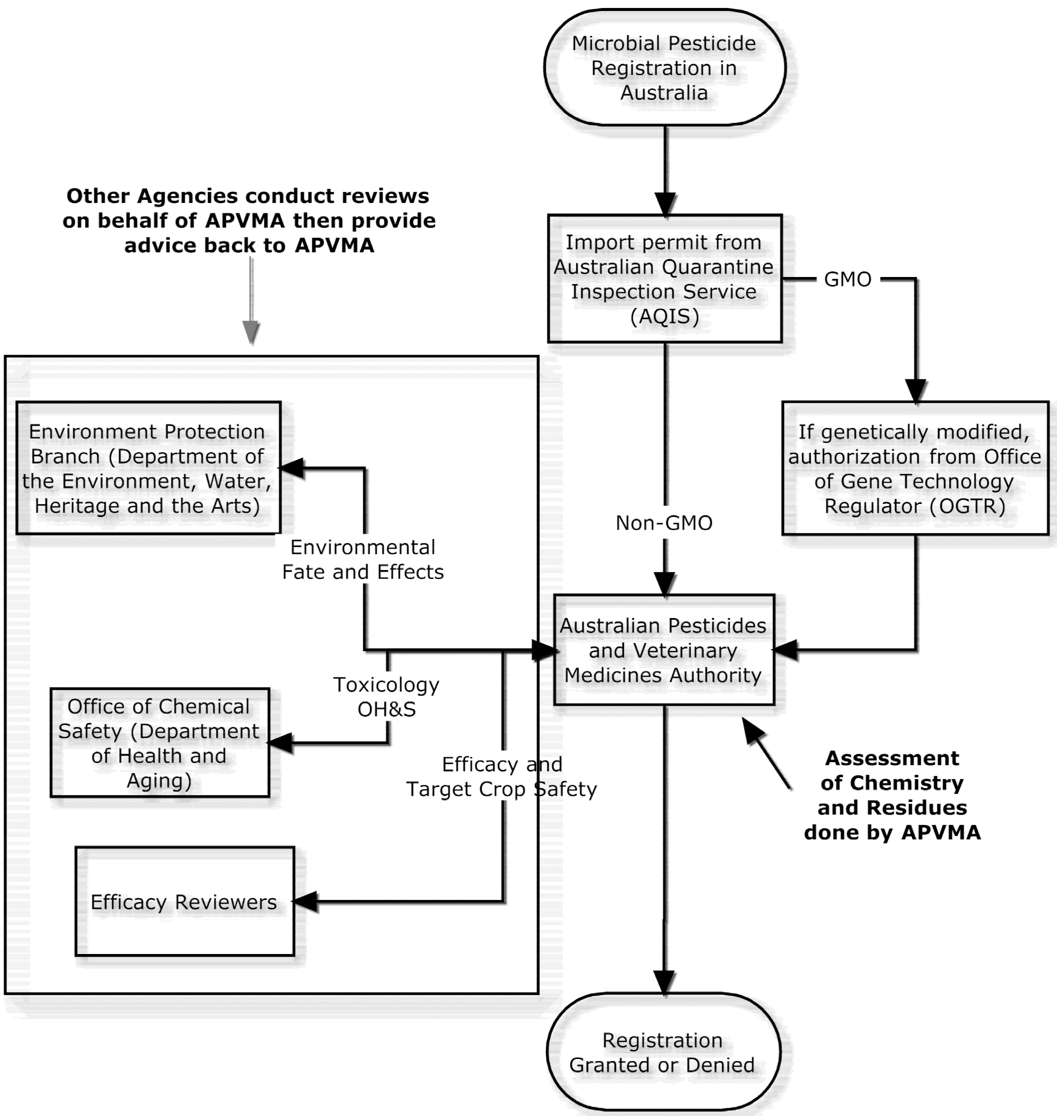

Figure 4. The process for registration of a new microbial pesticide in Australia.

The cost of registration can be prohibitive to microbial pesticides. The Australian market is estimated to be about 2-3% of the total global market for pesticides. Most microbial pesticides are used in niche situations with relatively small sales. Negative cash flows are experienced at the start of the registration process when investment needs to be made to pay the cost of local efficacy studies, additional studies specifically required for registration in Australia, and up-front payment of registration application fees. There are no fee reductions for registration of new products for minor uses, although a system does exist to obtain temporary permits for use of registered products in minor use situations. No income can be earned during the registration process, which can take several years. Thus the cost of registration can be high when comparing projected returns and pay-back times to those for broad-spectrum chemical insecticides.

The regulatory system is focussed on registration of synthetic chemical products, and has limited experience in registration of microbial pesticides due to the small number registered. As a result, applicants often find the process can involve unexpected requests for information not anticipated at the time of submission. These requests for additional, unexpected information can result in delays (which translate into delayed return on investment) as the applicant provides arguments to address the concerns, or can require further investment and time to undertake additional studies.

Assessments of a product application can take 15 months or longer. The registration of one microbial pesticide was delayed by a lack of understanding of the requirement for ingestion and field performance of a biological by the reviewer, which led to rejection of the initial efficacy package. The generation of supporting input from public and private researchers caused the loss of a full season of use and thus of a year's revenue. In the case of Green Guard the registration process took 4 years from the date of submission to the date of registration, and followed the classic synthetic insecticide pathway, with stringent requirements for residue data.

The Australian Government and the APVMA recognise there is a need to improve the regulatory system for novel products, including biopesticides. At the time of writing, the APVMA has established a working group to review the registration process for biopesticides, and the Australian Government is reviewing the operations of APVMA to determine how the process can be improved to authorise use of new products more quickly. It is anticipated that this will address many of the hurdles that currently prevent or delay registration in Australia.

SPECIAL CONCESSIONS AND ORGANIZATIONS PROMOTING BIOCONTROL

No special concessions are given to biopesticides during registration, although APVMA considers the benefits as well as risks of all pesticides. Microbial pesticides have demonstrated benefits in mainstream and niche applications in Australia, particularly in integrated pest management and sensitive environments. They can offer a 'low risk' alternative to chemical pesticides by helping to manage resistance to chemicals and reduced residues. These benefits can be offset against, for example, lower field efficacy. In addition, exemption for some data requirements can be made if a rational scientific case is made.

Consumer demand, workplace safety considerations and increased acceptance of the benefits of integrated pest and disease management will result in increased prospects for biopesticides. Much of Australia's fruit and vegetables are supplied to the consumer through supermarkets, which are demanding 'clean and green' and high quality produce. As a result, there is increasing use of protected structures (e.g. glasshouses, plastic covered poly-tunnels) to achieve the quality of vegetables demanded. There are restrictions on use of many synthetic chemical products in such protected structures due to concerns about exposure of workers to the products. At the same time, such structures commonly provide ideal environments for use of microbial pesticides. The increasing reliance on protected structures will see increasing use of lower risk products, including biopesticides.

Resistance to chemical insecticides continues to be of concern to industry, and biopesticides such as NPVs have demonstrated their value in strategies to minimise selection for resistance, prolonging the effective life of other pesticides. Secondary pest outbreaks are also a concern where disruption of natural enemies by application of broad-spectrum chemistry can lead to large scale and severe outbreaks (e.g. silver leaf whitefly and aphids in cotton). The selectivity of biopesticides enables them to be used without disrupting natural enemies, and so reduce secondary outbreaks.

Industry funding continues to support research into biopesticides, particularly from grains, cotton and horticulture industry bodies. The APVMA systematic review of chemical insecticides has led to withdrawal of many older chemicals, and more are expected to become unavailable for use in the future. The success of biopesticides combined with concerns over resistance and disruption of beneficial insect populations, and health risks to farm workers is leading to greater demand for biopesticides across industry.

Australia has demonstrated that good product quality, supply and distribution can create confidence and significant market demand by growers, which will increase opportunities for new products. Australia shares much in common with crops, pest species and climatic conditions in Asia, and offers excellent facilities and an excellent reputation for testing and data integrity. The Asian and Australasian market for microbial- and nematode-based pesticides was estimated to be worth approximately $132.5 million per annum in 2007/8, and opportunities exist that could raise the total market to $225 million by 2015 (CPL Business Consultants 2010).

SUMMARY

Australia is an island continent with a unique flora and fauna. Consequently, in addition to demonstrating a lack of undue hazard to humans, there is an emphasis on preventing entry of organisms that could have harmful effects on Australia's environment. The fate and specificity of biopesticides, including their capacity to induce epizootics or harmful effects on native species must be considered prior to introducing new microorganisms.

Australia has a small domestic market for insecticides, and microbial products are typically niche products within that market. Small projected returns and the lengthy registration process has limited the registration of microbial pesticides. However, at the time of writing, the registration process is under review with the specific goal of improving registration of such products.

The success of microbial pesticides in managing resistance and outbreaks of secondary pests in mainstream agricultural production such as cotton, sorghum and horticulture has demonstrated a role for biopesticides, and has created confidence and market demand based on quality and supply of products. Consumer demand for quality produce from ‘clean and green’ production systems and organic products, combined with growth in controlled-environment production, suggests there is a favourable future for biopesticides in Australia.

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